UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
CAMDEN VICINAGE

IN RE: VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION **This Document Relates to All Actions**	MDL No. 2875 Honorable Robert B. Kugler, District Court Judge Oral Argument Requested

DEFENDANTS' MEMORANDUM OF LAW IN OPPOSITION TO PLAINTIFFS' MOTION TO PRECLUDE THE OPINIONS OF DEFENSE EXPERT JANICE BRITT, PH.D.

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Federal Cases

Rules

Non-Periodical Publications

Pursuant to Federal Rules of Evidence 104, 403, and 702, Defendants' Executive Committee, on behalf of all Defendants in this litigation, submit this Memorandum of Law in Opposition to Plaintiffs' Motion to Preclude Opinions of Defense Expert Janice Britt, Ph.D.

INTRODUCTION

Plaintiffs seek to preclude the testimony and opinions of Dr. Janice Britt, Ph.D., by misrepresenting her deposition testimony and report and by misstating applicable law. The Court should reject this effort. Dr. Britt, a well-qualified toxicologist, used widely-accepted methods to arrive at her calculations and conclusions that the potential exposure to NDMA and/or NDEA detected in some batches of valsartan do not increase the theoretical risk of cancer above (1) endogenously formed NDMA or NDEA or (2) the background risk of cancer that everyone experiences.

Plaintiffs primarily attack Dr. Britt's qualifications and methods by claiming that Dr. Britt is not an *epidemiologist* and she did not conduct a systematic scientific literature search, as an epidemiologist would. This argument fundamentally misapprehends the role of a *toxicologist* in answering the question of general causation. A toxicologist focuses on dose-response relationships to assess the probability of a particular substance's toxicity under certain conditions, which Dr. Britt has done thoroughly in her report. Plaintiffs simply ignore major portions of

Dr. Britt's report, including, most critically, her conservative calculations that showed no meaningful excess risk of cancer from NDMA and/or NDEA in valsartan.

Plaintiffs also attempt to attack Dr. Britt's qualifications and methods by devoting significant effort to discrediting her colleagues and a framework they developed called evidence-based toxicology. Plaintiffs' discussion of evidence-based toxicology is a red herring and does not support her exclusion as an expert in this case because evidence-based toxicology was not the method Dr. Britt used to render her opinions in this case. For all of these reasons set forth more fully below, Plaintiffs' Motion should be denied.

SUMMARY OF RELEVANT OPINIONS

Dr. Britt's actual opinions are largely absent from Plaintiffs' Motion to exclude them. To be clear, in her report, Dr. Britt sets forth nine affirmative opinions relating to general causation:

- The overall body of scientific information shows no evidence of causation for NDMA or NDEA for cancer in humans. Furthermore, the plaintiffs' alleged exposure to NDMA and/or NDEA contained in valsartan does not increase cancer risk above the background risk incurred from other exposures to NDMA, NDEA, and other nitrosamines, or over the risk from other commonplace exposures to carcinogens Expert Report of Janice K. Britt, p. 28 ("Report") (Dkt. 1704-1, Exhibit D);

- The FDA and EMA Interim acceptable intakes for NDMA and NDEA involve a number of conservative assumptions and safety factors, such that the values derived cannot be viewed as the dividing line between "safe" and "unsafe" concentrations. Other safe doses for NDMA and

NDEA, based on up-to-date risk assessment methodology have been derived and provide more reliable values (Report, p. 33);

- The plaintiffs' estimated excess theoretical cancer risk from their reported exposure to NDMA and/or NDEA from valsartan products shows no increase over the excess cancer risk from exposure to NDMA formed naturally in the body (endogenous) or the background lifetime risk of developing cancer that everyone experiences (Report, p. 35);
- The plaintiffs' background exposure to NDMA, NDEA and other nitrosamines is orders of magnitude higher than the small concentrations of NDMA/NDEA that are potentially present in valsartan (Report, p. 44);
- The plaintiffs' alleged exposure and excess theoretical risk to NDMA and/or NDEA is within the background range that is considered acceptable by regulatory agencies (Report, p. 50);
- The extrapolation of animal test results to predict the actual human response is a regulatory assumption associated with great uncertainty (Report, p. 53);
- Scientific evidence exists to show that NDMA and NDEA have thresholds (Report, p. 56);
- The human body contains multiple repair mechanisms that help overcome one's exposure to chemicals (Report, p. 57); and
- The plaintiffs' alleged excess theoretical risk associated with exposure to NDMA and/or NDEA from use of valsartan is lower than the background cancer risks we all face (Report, p. 60).

Dr. Britt further renders the following rebuttal opinions in response to Plaintiffs' experts, Dr. Stephen Lagana, MD, and Dr. Dipak Panigrahy, Ph.D.:

- The evidence does not support Dr. Lagana's prediction that the dose-response curve for cancer from NDMA becomes non-linear and results in "more potency" and "more cancers" at 120 ng/daily intake,

as endogenous formation of NDMA exceeds this number (Report, p. 91);

- There is no evidence to support Dr. Lagana's statement that "anyone who has consumed . . . contaminated valsartan has assumed an unreasonable oncological risk" because NDMA or NDEA are not known human carcinogens, the hypothetical "worst-case" exposures from valsartan containing an NDMA or NDEA impurity do not result in any unacceptable excess risk, and all potential excess risks are theoretical (Report, p. 91);

- In his discussion of the role of inflammation in cancer, Dr. Panigrahy fails to consider other large known risks for inflammation and cancer, such as alcohol, tobacco, asbestos, and other chemicals. He also fails to compare those risk factors to the small theoretical risk that the alleged exposures in this case may present (Report, pp. 91-92);

- Dr. Panigrahy opines without basis that NDMA and NDEA are synergistic compounds (Report, p. 92); and

- Dr. Panigrahy improperly relies on a study by Hidajat et al., an occupational study of British rubber workers that evaluated inhalation exposure to a variety of chemicals and compounds and has numerous shortcomings, including a failure to control for confounders (Report, p. 92).

ARGUMENT

I. LEGAL STANDARD

Rule 702 provides that a witness "qualified as an expert by knowledge, skill, experience, training or education" may testify if:

> (a) the expert's scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue; (b) the testimony is based on sufficient facts or data; (c) the testimony is the product of reliable principles and methods; and (d) the expert has reliably applied the principles and methods to the facts of the case.

Fed. R. Evid. 702. "The Rules of Evidence embody a strong preference for admitting any evidence that may assist the trier of fact." *Pineda v. Ford Motor Co.,* 520 F.3d 237, 243 (3d Cir. 2008).

The Third Circuit has clarified that Rule 702 "embodies a trilogy of restrictions on expert testimony: qualification, reliability, and fit." *Ruggiero v. Yamaha Motor Corp., U.S.A.*, 778 F. App'x 88, 93 (3d Cir. 2019) (citing *Schneider ex rel. Estate of Schneider v. Fried*, 320 F.3d 396, 404 (3d Cir. 2003)). Therefore at this stage of the litigation, the relevant question "is not whether [Dr. Britt] [is] right. The question is whether [Dr. Britt] [has] offered opinions that would be admissible at a jury trial." *In re Roundup Prod. Liab. Litig.,* 390 F. Supp. 3d 1102, 1108–09 (N.D. Cal. 2018).

While defendants bear the burden of showing "by a 'preponderance of proof' that [Dr. Britt] is qualified and will testify to scientific knowledge that will assist the trier of fact in understanding and disposing of issues relevant to the case," *Pride v. BIC Corp.,* 218 F.3d 566, 578 (6th Cir. 2000), defendants do not, however, bear the burden of proof on general causation. *See Holbrook v. Lykes Bros. S.S. Co.*, 80 F.3d 777, 786 (3d Cir. 1996) (noting that, although expert's testimony would have been insufficient to prove causation, the defense did not bear this burden). Therefore, a defense expert such as Dr. Britt has no obligation to "offer a competing general causation opinion" and may offer an opinion that "criticiz[es] the analysis and

conclusions presented by another party." *See In re Abilify (Aripiprazole) Prods. Liab. Litig.*, 299 F. Supp. 3d 1291, 1368 (N.D. Fla. 2018).

A. Dr. Britt Is Well-Qualified To Offer Her Opinions

1. Dr. Britt is A Qualified Toxicologist

Plaintiffs' attacks on Dr. Britt's qualifications have no basis in fact or law. Dr. Britt is eminently qualified in the field in which she seeks to offer opinions, toxicology. As set forth in her report and CV, Dr. Britt is a managing scientist at ToxStrategies, Inc., which specializes in toxicology, including the assessment of chemical exposures and their associated hazards or risks. Report, p. 13; CV, p. 1. Dr. Britt has more than 20 years of experience in toxicology and has expertise in the specific areas of human and animal toxicology, chemical exposure assessment, dose-response analysis, and risk assessment. Report, p. 13; CV, p. 1. Dr. Britt holds a bachelor's degree in Zoology from Texas A&M University and a doctorate in Toxicology from Texas A&M University's College of Veterinary Medicine and Biomedical Society. Report, p. 13; CV, p. 2.

Dr. Britt has developed toxicological profiles for various chemicals and evaluated the appropriateness of various regulatory toxicology criteria, which includes calculation of reference doses, cancer slope factors and occupational exposure guidelines. Report, p. 13; CV, p. 1. Dr. Britt also has extensive experience

in the areas of systematic literature review, causation analysis, and evidence-based toxicology. Report, p. 13.

Dr. Britt is a member of the Environmental Protection Agency's Human Studies review board, a federal advisory committee that provides advice and recommendations on issues of human subject research. Report, p. 13; CV, p. 2. She also holds professional associations with the Society of Toxicology, Risk Assessment Specialty Section; the Society for Risk Analysis, The American Conference of Governmental Industrial Hygienists, and EUROTOX. She is a European Registered Toxicologist and a Fellow of the Royal Society of Biology. Report, p. 14, CV, p. 2.

Dr. Britt has authored numerous articles, including a recently published 10-year retrospective on the use of evidence-based methods in assessing causation in toxicology. Report, p. 13; CV, p. 1. She is a peer reviewer for the following publications: *Regulatory Toxicology and Pharmacology*, *Food and Chemical Toxicology*, *European Journal of Obstetrics & Gynecology and Reproductive Biology*, and *Human and Experimental Toxicology*. CV, p. 2.

Contrary to Plaintiffs' attempts to portray Dr. Britt as simply a "litigation expert," the majority of her work is for clients outside of litigation. Transcript of the

Deposition of Janice K. Britt, Ph.D. (hereinafter, "Tr."), 139:17-140:11.[1] She estimates that 40% of her work has been with regulatory agencies, while 20% of her work has involved litigation. Her remaining work includes non-litigation work with private companies in the consumer products, food supply, and pharmaceutical industries. Tr., 140:13-142:16.

Despite Dr. Britt's impressive credentials, Plaintiffs first argue she is not qualified because "she is not an expert in, or providing opinions in the fields of epidemiology, medicine, or regulation." Motion, p. 5. Under Rule 702, however, "[t]he nature of a witness's specific field of expertise is part of the expert's background that is considered in determining whether a witness is qualified." *In Re Paoli R.R. Yard PCB Litig.*, 35 F.3d 717, 741 (3d Cir. 1994). Dr. Britt readily admitted that she is not an epidemiologist or medical doctor, and she is not offering epidemiology or medical opinions. She noted that Defendants have offered *other* experts to render those opinions. Tr. 82:18-83:10; 90:16-91:6; 91:7-17.

As Dr. Britt explained, however, toxicologists regularly evaluate epidemiology studies as part of their analyses. Tr., 90:16-91:6 (Q: Am I correct that you're limiting your opinions in this case to opinions formed in the field of toxicology? Mr. Gallagher: Objection to form. The Witness: Yes, I am, with the

[1] A true and accurate copy of the transcript of the deposition of Janice K. Britt, Ph. D., dated September 23, 2021, is attached to the Certification of Seth A. Goldberg, Esq., as Exhibit A.

caveat that if I evaluated, you know, like I said, an epi paper or a human health paper that also falls within the realm of toxicology, because we also evaluate epi papers. But I am a toxicologist. That is my field."); *see also* Reference Manual on Scientific Evidence, at 657 (3d Ed. 2011) ("Reference Manual") ("Clearly, both epidemiology and toxicology have much to offer in elucidating the causal relationship between chemical exposure and disease.") Dr. Britt's limited evaluation of certain epidemiological or human health studies therefore falls squarely within her area expertise. It simply does not follow that, because Dr. Britt incorporated some epidemiological data into her overall analysis of scientific literature on NDMA and NDEA, she is unqualified to offer her toxicology opinions.

Plaintiffs next argue Dr. Britt is unqualified because she lacks pre-litigation experience with NDMA or NDEA and was "barely aware . . . if at all" of the valsartan recall before her engagement. Motion, p. 16. First, to the extent even relevant to her qualifications, neither statement is true. Dr. Britt specifically testified that she was in fact aware of the recall. *See* Tr., 171:13-172:4 ("Q. When did you first become aware of the contamination of valsartan with NDMA and NDEA? Mr. Gallagher: Objection to form. The Witness: I do not recall the specific date. Q. Did you know about it before you were contacted to work in this litigation? Mr. Gallagher: Objection to form. The witness: I believe I – I had seen it in the news or CNN.com."). Dr. Britt also has some experience as a consultant evaluating NDMA

and nitrosamine exposure, as she calculated the toxicity of nitrosamines related to a litigation involving a munitions plant. Tr., 41:7-43:9; 86:7-24; CV, p. 9.[2] Plaintiffs' willingness to misrepresent the factual record undermines the credibility of their

[2] Although Plaintiffs correctly point out that Dr. Britt could not recall her engagement in the munitions matter 15 years ago in detail, the expert opinion on which Dr. Britt worked as a consultant is publicly available and entirely consistent with her opinions here. That opinion – deemed admissible by the Court – stated, in relevant part:

> Thus, it is important to recognize that everyone is exposed on a daily basis to dimethylnitrosamine (NDMA) and other preformed nitrosamines. The presence of dimethylnitrosamine in our daily environment has been relatively well-characterized, and it has been found in a variety of foods including vegetables, cheese, beer, and cured meets; in shampoos, hair conditioners, shower gels, bath oils, and facial cleansers; in tobacco products; in therapeutic drugs including tablets, suppositories, injections, drops and syrups; and in technical and commercial pesticides used in agriculture, hospitals, and homes.
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> In addition to exposure to preformed nitrosamines, everyone continuously produces NDMA and other nitrosamines in their gastrointestinal tracts (predominantly in the stomach and small intestine) from the reaction of nitrite with nitrosatable species. This process is referred to as endogenous production. In this process, nitrite can react with dimethylamine to form NDMA or with other nitrosatable species to form numerous nitroso-compounds. The majority of ones' body burden of nitrite is usually derived from the metabolism of dietary and endogenously produced nitrate rather than from the direct consumption of nitrite.

The Report of Dr. Robert C. James & Dr. Philip S. Guzelian, *In the Matter of Bates, et al., v. Ensign-Bickford Industries, et al.* No. 99Cv00120, 1999 WL 34002562 (D. Utah 1999).

entire Motion.[3] Second, even were Plaintiffs' statements true, Rule 702 does not demand that a scientific expert complete independent, pre-litigation research or work so long as she is otherwise qualified in her field. *See In re Hum. Tissue Prod. Liab. Litig*., 582 F. Supp. 2d 644, 670 (D.N.J. 2008). Indeed, Plaintiffs fail to cite any authority that might support preclusion of Dr. Britt's opinions on this basis. Further, under the fabricated standard that Plaintiffs propose, none of their own experts would be permitted to testify because they – unlike Dr. Britt – have no prior experience researching NDMA or NDEA.

As a last-ditch effort to exclude Dr. Britt based on qualifications, Plaintiffs suggest to the Court that her credibility is compromised because work performed by her ToxStrategies colleagues in other *unrelated* matters has been criticized. Motion, p. 2, n. 1; pp. 6-8. This "guilty by association" argument is unfounded and inappropriate. Dr. Britt made clear at her deposition that she herself did not work on the projects or reports cited by Plaintiffs, nor did she have any awareness of them. Tr. 180:5-181:15; 189:2-191:24; 192:10-194:14. Clearly, those matters have no bearing on Dr. Britt's qualifications.

B. <u>Dr. Britt Employed A Reliable Methodology</u>

[3] This is one of many examples throughout Plaintiffs' brief in which they inaccurately paraphrase, selectively quote, or misrepresent Dr. Britt's testimony, all without providing her actual testimony to the Court.

In arguing for Dr. Britt's exclusion, Plaintiffs misapprehend how the science of toxicology relates to general causation. Toxicology studies the adverse effects that chemical, physical, or biological agents (toxicants) might induce in biological symptoms. Report, p. 19; *White v. Esmark Apparel, Inc.*, 44 F.3d 1005 (5th Cir. 1995) ("Toxicology is 'a science that deals with poisons and their effect on living organisms [and] with substances otherwise harmless that prove toxic under particular conditions[.]'"). The dose-response relationship is universally acknowledged as a "hallmark of toxicology":

> [T]he relationship between dose and effect (dose-response relationship) is the hallmark of basic toxicology. Dose is the single most important factor to consider in evaluating whether an alleged exposure caused a specific adverse effect. Often low dose exposures—even for many years—will have no consequence at all, since the body is often able to completely detoxify low doses before they do any damage. Furthermore, for most types of dose-response relationships following chronic (repeated) exposure, thresholds exist, such that there is some dose below which even repeated, long-term exposure would not cause an effect in any individual."

McClain v. Metabolife Intern., Inc., 401 F.3d 1233, 1242 (11th Cir. 2005).

Thus, under the Rule 702 framework, a qualified toxicologist's opinion on causation should include three preliminary assessments: (1) whether the disease can be related to chemical exposure by a biologically plausible theory; (2) whether the plaintiff was exposed to the chemical in a manner that can lead to absorption into the body; and (3) whether the dose to which the plaintiff was exposed is sufficient to cause the disease. Reference Manual at 661; *see In re Roundup Prod. Liab. Litig.,*

390 F. Supp. 3d 1102, 1111 (N.D. Cal. 2018) (citing *Anderson v. Liberty Lobby, Inc.,* 477 U.S. 242, 249-50 (1986) ("To carry their burden during this phase of the litigation, the plaintiffs must put forward admissible evidence supporting their claim that [a substance] is capable of causing [the alleged disease] at exposure levels humans might have experienced.")); *see also Hardeman v. Monsanto Co.*, 997 F.3d 941, 963 (9th Cir. 2021); *In re Zoloft (Sertralinehydrochloride) Prod. Liab. Litig.*, 26 F. Supp. 3d 483, 487 (E.D. Pa. 2016), *aff'd sub nom. In re Zoloft (Sertraline Hydrochloride) Prod. Liab. Litig.*, 858 F.3d 787 (3d Cir. 2017); *In re Viagra (Sildenafil Citrate) & Cialis (Tadalafil) Prod. Liab. Litig.*, 424 F. Supp. 3d 781, 793 (N.D. Cal. 2020) (quoting *In re Hanford Nuclear Rsrv. Litig.*, 292 F.3d 1124, 1133 (9th Cir. 2002)).

A reliable methodology should also consider the background risk, which is "the risk that everyone faces of suffering the same malady that a plaintiff claims without having exposure to the same toxin." *McClain*, 401 F.3d at 1243. *see also Chapman v. Procter & Gamble Distrib., LLC*, 766 F.3d 1296, 1307 (11th Cir. 2014) (excluding expert general causation opinions where experts did not know the background risk of the relevant disease); *Abilify*, 299 F. Supp. 3d at 1308 ("[A] failure to identify or describe the background risk of a disease is a "serious methodological deficiency" and "substantial weakness" in an expert's general causation opinion.); *In re Denture Cream Prod. Liab. Litig.*, 795 F. Supp. 2d 1345,

1365 (S.D. Fla. 2011) (noting that without a baseline of the background risk of a disease, "any incidence could be a coincidence").

Unlike Plaintiffs' experts, Dr. Britt offers toxicology opinions that meet all of the above criteria. Dr. Britt's methodology involved four main components: (1) a detailed review of available scientific literature concerning the carcinogenicity of NDMA and NDEA, including animal studies and epidemiological (human) data (Report, pp. 28-32; 53-56); (2) a detailed review of available scientific literature concerning the background risk of cancer (Report, pp. 60-90); (3) a comparative analysis of potential excess cancer risk based on the FDA's valsartan data, using widely-accepted risk calculation methods (Report, pp. 35-49); and (4) an analysis and rebuttal of certain of Plaintiffs' experts' opinions (Report, pp. 91-92).

By ignoring Dr. Britt's other methods and opinions, Plaintiffs seek to focus solely on Dr. Britt's literature review and then claim the principles of evidence-based toxicology were neither reliable nor reliably applied. Not only are such criticisms invalid but, in all events, they are insufficient to warrant Dr. Britt's exclusion because they do not address the full scope of Dr. Britt's opinions and testimony.

1. Dr. Britt's Methods Included A Thorough Review Of All Relevant Scientific Literature.

Dr. Britt's 92-page report makes clear that she undertook a thorough review of relevant scientific literature to inform her opinions, including a review of human valsartan and related pharmaceutical data (Report, pp. 29-32; Tr. 242:6-243:12),

animal studies (Report, Appendix A; Tr. 257:20-258:13) and regulatory information concerning NDMA and NDEA (Report, pp. 25, 32-34), as well as voluminous data on background cancer risk and exposures (Report, pp. 60-90). This review formed the basis of her opinions that insufficient data exists to conclude that NDMA and NDEA are known human carcinogens, that any risk of cancer in humans from NDMA/NDEA exposure was merely theoretical, and that the theoretical excess risk was orders of magnitude lower than the risk of cancer from background exposures. Report, pp. 28-32; 35-52.

2. Dr. Britt Used Widely Accepted Calculation Methods To Conclude That NDMA- and NDEA-Containing Valsartan Present No Excess Risk of Cancer.

Dr. Britt's methodology did not start and end with a literature review, as Plaintiffs seek to imply. Rather, as a toxicologist, she developed her opinions by calculating theoretical excess cancer risk from alleged exposures to NDMA and NDEA in this case compared with background risk. Report, pp. 35-49; 60-90. Dr. Britt employed widely-accepted methods for each of these calculations.

Using the FDA's data and conservative assumptions, Dr. Britt calculated the lifetime average daily dose (LADD) and excess cancer risk for low and maximum average NDMA- and NDEA-containing valsartan for each of the six manufacturing defendants, Prinston, Aurobindo, Hetero, Mylan, Teva and Torrent. Report pp. 37-38. She further calculated combined excess cancer risks off NDMA and NDEA. *Id.*

Based on these calculations, she concluded that, even if a patient took medications from one or more manufacturers at different points in time, it is unlikely that their theoretical excess cancer risk would have resulted in a significantly increased risk above background. She further concluded that all theoretical excess cancer risks are within the 10^{-4} to 10^{-6} acceptable risk range used by many regulatory bodies. Report, pp. 35-36; 50-53. Dr. Britt also calculated lifetime excess cancer risk from valsartan containing NDMA and NDEA compared to other background cancer risks and concluded that the plaintiffs' actual background risk of developing cancer is up to ***more than five million times higher*** than any theoretical risk from exposure to NDMA or NDEA from valsartan. Report, p. 43.

3. Dr. Britt Properly Based Her Rebuttal Opinions To Plaintiffs' Experts On Her Background And Experience

Dr. Britt's rebuttal opinions to Plaintiffs' experts are valid and admissible opinions under Rule 702. In the final section of her report, Dr. Britt reviewed the expert reports of Dr. Panigrahy and Dr. Lagana and explained various flaws in their methodologies, including Dr. Lagana's improper assumptions that *no* dose of NDMA or NDEA is safe for humans and Dr. Panigrahy's misplaced reliance on a single epidemiological study. Report, pp. 91-92.

As a rebuttal expert, Dr. Britt was entitled to rely on her background and experience to rebut Plaintiffs' experts' opinions. *In re Mirena IUD Prods. Liab. Litig.*, 169 F. Supp. 3d 396, 418-19 (S.D.N.Y. 2016) ("pointing to the absence of

convincing studies or the weaknesses of studies on which [p]laintiffs rely, and evaluating them in light of their … experience, training and research, is … a logical and valid approach" to responding to plaintiffs' experts' opinions); *In re Zyprexa Prods. Liab. Litig.*, 489 F. Supp. 2d 230, 285 (E.D.N.Y. 2007) (noting that defense experts "have no burden to produce models or methods of their own; they need only attack those of plaintiffs' experts.") As a result, it is "entirely appropriate" for Dr. Britt to offer "critiques of [p]laintiffs' experts' evidence, methodologies, and conclusions." *Abilify*, 299 F. Supp. 3d at 1368.

4. Evidence-Based Toxicology Was Not Dr. Britt's Methodology In This Case.

Without addressing any of the methods described above, Plaintiffs misrepresent that evidence-based toxicology is the foundation of all of Dr. Britt's opinions and testimony. *See* Motion, pp. 6-9, 13-16. While Dr. Britt has expertise in evidence-based toxicology, her report makes clear that she did not use evidence-based toxicology to develop her opinions in this case. In fact, the only mention of evidence-based toxicology in her report is in the qualifications section. *See* Report, p. 13. Plaintiffs' attempt to pigeon-hole Dr. Britt into a single, mislabeled method falls flat.

Regardless, because Plaintiffs seek to discredit Dr. Britt by mischaracterizing one area of her expertise as junk science, some clarification of evidence-based toxicology's principles is warranted. Evidence-based toxicology has been used by

toxicologists for more than 15 years and has expanded in the field of toxicology in that timeframe. Tr. 232:9-233:19. Evidence-based toxicology's roots are in evidence-based medicine, a concept that is widely recognized by the scientific community. Tr., 215:5-17. (Q: Okay. The next thing that I'd like to ask you about is evidence-based toxicology. First question is, what is evidence-based toxicology as you use that term? A: Evidence-based toxicology is basically – has its basis in evidence-based medicine, which has been around a fairly long time. But it's still used by physicians in forming opinions on treatment methods and treatment regimens for patients…."). Following the same evidence-based logic as applied to medicine, Dr. Britt explained that evidence-based toxicology is a method by which a scientist considers all available studies and sets forth with particularity how each study was ranked and considered. Tr., 216-:9-217:1. This process permits other scientists to evaluate the methodology, replicate it, and test the conclusions reached. Tr., 217:9-13. ("A:. . . [s]o it's basically meant to be a transparent methodology that's systematic that if it's out there, anyone that follows should be able to come to the same conclusions that you do.") In other words, "evidence-based toxicology" is a term used to describe systematic review processes that scientists have long employed.

Nonetheless, Plaintiffs attempt to discredit all of Dr. Britt's opinions using a selectively quoted eight-page article that criticizes evidence based toxicology, the

Rudén/Hansson article. Motion, pp. 6-9. First, any criticism in the Rudén/Hansson article would, at most, go to weight, not admissibility. *See Heller v. Shaw Industries, Inc.*, 167 F. 3d 146, 160 (3d Cir. 1999); *Ruiz-Troche v. Pepsi Cola*, 161 F. 3d 77, 85 (1st Cir. 1998) ("Daubert neither requires nor empowers trial courts to determine which of several competing scientific theories has the best provenance."). Second, the Rudén/Hansson article primarily takes issue with evidence-based toxicology's application in regulatory risk assessments, which are not relevant here. *See* Rudén/Hansson at 299 ("If [evidence-based toxicology] were to be implemented it would have drastic implications for current risk assessment practices."); 301 ("If [evidence-based toxicology] were to be implemented for the purpose of toxicological risk assessment, this would have radical implications for public health."). Dr. Britt is evaluating general causation, not regulatory risk. In her Opinion #2, Dr. Britt draws a clear distinction between the goals and approaches of a regulatory body in determining "safe" threshold doses compared with the question of general causation:[4]

> Regulatory bodies typically take a conservative approach in developing safe exposure levels for chemical-induced effects. They use the toxicity data for the chemical they are evaluating (e.g., an animal toxicity test) and use it to extrapolate to a corresponding safe dose in humans.

[4] While Dr. Britt testified that some regulatory agencies, such as the EPA, have started using systematic reviews to ensure they are using a consistent, repeatable method and to promote transparency, she made clear that those agencies do not employ evidence-based toxicology, consistent with her Report. Tr., 226:22-228:10; 235:13-236:5.

> Because all exposures that produce doses less than the threshold dose (or a NOAEL) should be devoid of toxicity, all exposure below these points are meant to represent safe exposure levels, even though these levels are not bright lines between safe and unsafe. However, when extrapolating from animal data, as must typically be done in toxicology, there is always some uncertainty as to how closely the animal dose-response quantitatively and qualitatively mimic the actual human dose-response curve. As a conservative approach then, safety/uncertainty factors are selected, and the NOAEL/threshold dose is divided by a total safety/uncertainty factor from a combination of different uncertainty factors that each reflects the uncertainty of the dose-response data being used in the extrapolation."

Report, p. 25.

Moreover, courts have also long drawn the distinction between regulatory risk analysis and general causation:

> The risk-utility analysis [undertaken by agencies like FDA] involves a much lower standard than that which is demanded by a court of law. A regulatory agency such as the FDA may choose to err on the side of caution. Courts, however, are required under the *Daubert* trilogy to engage in objective review of evidence to determine whether it has sufficient scientific basis to be considered reliable.

McClain, 401 F.3d at 1249-50 (internal citation omitted); *see also Denture Cream*, 795 F. Supp. at 1365 ("[R]egulatory agencies follow different standards than courts in toxic-tort cases."); *In re Neurontin Mktg., Sales Pracs., & Prod. Liab. Litig.*, 612 F. Supp. 2d 116, 136 (D. Mass. 2009) ("It is widely recognized that, when evaluating pharmaceutical drugs, the FDA often uses a different standard than a court does to evaluate evidence of causation in a products liability action.").

Consistent with these standards, Dr. Britt's opinions focus on the general causation question with which this Court is concerned, not regulatory risk. Plaintiffs' focus on evidence-based toxicology and the Rudén/Hansson article is misplaced.

C. Dr. Britt Reliably Applied Her Methodology

1. Dr. Britt Appropriately Relied On The Systematic Literature Reviews By Defendants' Epidemiologists

In arguing that Dr. Britt failed to apply her own methods, Plaintiffs distort her testimony about her reasons for not having conducted a "systematic" literature review. In fact, Dr. Britt specifically explained that she relied on the systematic literature reviews by Defendants' epidemiology experts, Dr. Fryzek and Dr. Gibb, *because those experts used a verifiable, repeatable methodology*. Tr., 150:3-16 ("In reading the reports, did you determine that any of the experts for either side did perform a systematic review, whether they called it that or not? Did you see anybody perform a systematic review? MR. GALLAGHER: Object to form. THE WITNESS: I mean, in reviewing, for example, Dr. Fryzek's expert report as far as epi evidence, it appeared that he used methods that you would use in a systematic review.");83:11-20 (Q: And your report specifically referred to the defense expert epidemiologists. Why didn't you also defer to the plaintiff expert epidemiologists? MR. GALLAGHER: Objection to form. THE WITNESS: I – ultimately I agreed more with the methodology of the defense expert.") In particular, Dr. Britt was able to trace and credit the findings of the Pottegard and Gomm studies that there was no

increased risk for cancer based on NDMA-containing valsartan.[5] Report, pp. 29-32.[6] Moreover, nothing about this reliance renders her opinions inadmissible because Rule 702 specifically permits experts to use consultants or other experts in technical areas outside of their expertise. *See, e.g., Dura Auto. Sys. of Ind., Inc. v. CTS Corp.,* 285 F.3d 609, 613 (7th Cir. 2002)("[I]t is common in technical fields for an expert to base an opinion in part on what a different expert believes on the basis of expert knowledge not possessed by the first expert."); *Titan Stone, Tile & Masonry, Inc. v. Hunt Constr. Grp., Inc.*, 2007 WL 1659056, at *3-4 (D.N.J. June 5, 2007) (rejecting argument that expert opinion should be excluded because expert incorporated into his report the schedule analysis of an unsworn, undesignated expert, noting that "[a]n expert witness is permitted to use assistants in formulating his expert opinion"). Accordingly, the notion that Dr. Britt needed to engage in a separate, "systematic" literature review falls flat.

2. Dr. Britt Reviewed and Considered All Relevant Data

[5] To the extent Plaintiffs suggest this was not a "reliable" application of evidence-based toxicology – which was not Dr. Britt's method –Dr. Britt's reliance on the other defense experts' systematic literature was fully in line with the principles of a systematic, repeatable method, not in contrast to them.

[6] Dr. Britt did not concede that she was unqualified to review the epidemiology studies– quite the opposite. She stated that she is able to evaluate study design and overall conclusions, and only deferred to other experts for in-depth review of those studies. Tr. 244:1-19.

Plaintiffs' other criticisms of Dr. Britt's literature review, including that she failed to consider certain data, are simply inaccurate and, beyond that, relate to Plaintiffs' disagreements with Dr. Britt's conclusions as opposed to her methods. Plaintiffs' disagreement with Dr. Britt's conclusions is not a basis under Rule 702 for excluding Dr. Britt's opinions.

For example, Plaintiffs claim that Dr. Britt failed to consider animal data in concluding that insufficient evidence exists to support that NDMA and NDEA are human carcinogens. Motion, pp. 10-11. This is not true: Dr. Britt *did* evaluate animal studies in her report, including the Peto studies. Report, pp. 33-34. Tr. 256:11-19. Dr. Britt also explained in her Opinion #6 the significant shortcomings with extrapolating from animal data to humans – shortcomings that toxicologists recognize when performing a causation analysis, and many courts have also recognized. *See* Report, pp. 53-56 ("The extrapolation of animal test results to predict that actual human response is a regulatory assumption associated with great uncertainty."), Appendix A; Tr. 257:20-258:13; *Paoli II,* 35 F. 3d at 743 ("[T]he use of animal studies may not be methodologically acceptable to show that chemical X increases the risk of cancer in humans because, for example, the doses used to induce responses in animals are almost always significantly higher than the exposure humans face. . . for animal studies to be admissible to prove causation in humans, there must be 'good grounds to extrapolate from animals to humans, and the

methodology of the studies must constitute good grounds to reach conclusions about the animals themselves.'"). Put simply, Dr. Britt did not ignore animal data as Plaintiffs suggest – she simply reached a different conclusion than Plaintiffs' experts.

As discussed above, Dr. Britt also explained that she did not rely on regulatory authorities' determinations about risk because such authorities seek to make determinations relating to public health rather than causal determinations. Report, pp. 25, 32-34. Incongruously, Plaintiffs argue not only that Dr. Britt neglected to consider regulatory risk assessments but also that she somehow conceded general causation by "validating" IARC's classification of NDMA and NDEA as Class 2A Probable Human Carcinogens. Motion, p. 5. Putting aside that, logically, both cannot be true, IARC's classifications are not equivalent to scientific proof of general causation. Yet, Plaintiffs misrepresent and misquote Dr. Britt's testimony about IARC in an effort to create the impression that she somehow "conceded" general causation:

> Q: The hypothesis that NDMA is a probable human carcinogen is not novel, correct?
>
> Mr. Gallagher: Object to form.
>
> The Witness: It is a – you know, regulatory agencies such as IARC and EPA have classified it as a, you know probable human carcinogen, based on animal data, not based on – **it's not a known human carcinogen. There's not sufficient data to conclude that it's a human carcinogen.**

Tr., 198:21-199:6.

Plaintiffs' distortion of the record is not grounds for exclusion.

D. Dr. Britt's General Causation Opinions Fit This Case, and Plaintiffs Do Not Argue Otherwise

Dr. Britt emphasized in her report the importance of considering dose and duration of exposure to a substance in determining an association with a particular outcome – a hallmark of toxicology principles. *McClain*, 401 F.3d at 1242 (discussing dose response relationship); *see* Report, p. 33. This emphasis aligns with the legal principle that the general causation inquiry in product liability cases must take into account the dose and duration that plaintiffs may reasonably expect to have consumed or experienced. *Id.* Accordingly, Dr. Britt's opinion that NDMA and NDEA do not cause cancer in humans at the dose and duration of exposure experienced by Plaintiffs in this case "fits" with the general causation question and, as such, will certainly assist the trier of fact.

Plaintiffs do not, nor can they, argue that taking into account dose and duration is inappropriate in this case or in the field of toxicology in general. Instead, Plaintiffs seem to avoid the issue altogether by launching unsupported attacks on her qualifications and methodology, as set forth above. Indeed, Plaintiffs would prefer that the Court *not* focus on the key concepts of dose and duration because their own experts failed to take these into account when presenting their own overly generalized opinions that NDMA and NDEA are carcinogenic through any exposure

method, at any level, and for any period of time. Plaintiffs' attacks do not support exclusion of Dr. Britt's opinions and should be rejected.

CONCLUSION

For the reasons set forth above, Defendants respectfully request that this Court deny Plaintiffs' Motion to Exclude the Testimony of Dr. Janice Britt.

Dated: December 1, 2021

Respectfully Submitted by the Defense Executive Committee on behalf of all Defendants,

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CERTIFICATE OF SERVICE

I HEREBY CERTIFY that on December 1, 2021, I electronically filed the foregoing with the Clerk of the Court by using the CM/ECF system which will send a notice of electronic filing to all CM/ECF participants in this matter.

/s/ Seth A. Goldberg
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